Final-7/2/73 Teratologic Evaluation of FDA 71-16 (Guar Gum) in Rabbits

FDA 15

FOOD AND DRUG
LABORATORIES, INC.

MAURICE AVENUE AT 58TH STREET, MASPETH, NEW YORK 11378

FINAL

July 2, 1973

Teratologic Evaluation of FDA 71-16

(Guar Gum)

in

Rabbits

FOOD AND DRUG Research LABORATORIES, INC.

Reply to
WAVERLY DIVISION
Route 17
P.O. Box 107
Waverly, New York 14892
(607) 565-2931

July 2, 1973

Mr. L. C. Appleby, Contracts Officer
Deaprtment of Health, Education and Welfare
Food and Drug Administration
Contracts Section CA-272
Contracts and Grants Branch
5600 Fishers Lane
Rockville, Maryland 20852

COPY

Subject: Teratologic Studies, Final Report (One Species-Rabbits)
Re: FDA Contract No. 71-260

Dear Mr. Appleby:

We are today forwarding final reports covering teratologic studies on FDA Compounds 71-16 and 71-17 in rabbits. The disposition of the reports is as follows:

Your office	1 copy (via Mr. Carle's office)
Dr. Alan Spiher	2 copies
Dr. Joseph McLaughlin	2 copies

These final copies correspond to drafts dated May 31, 1973.

If you have any further instructions, or questions, please do not hesitate to contact us.

Cordially,

FOOD and DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

KM:smm

cc: Dr. Alan Spiher
Dr. Joseph McLaughlin
Mr. D.A. Carle

RABBITS

Food and Drug Research Laboratories
INCORPORATED

Maurice Avenue at 58th Street
Maspeth, New York 11378
Telephone: TWining 4-0800
Cable: Foodlabs, New York

FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 2, 1973

Laboratory No. 0896 f
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-16 (Guar Gum)

Examination Requested: Teratologic evaluation of FDA 71-16 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion: On the basis of the data presented herein, the following conclusion appears warranted:

"The administration of up to 700 mg/kg (body weight) of the test material as a suspension in anhydrous corn oil to pregnant rabbits for 13 consecutive days had no obvious effect on nidation or on fetal survival of implanted embryos. The number and type of abnormalities seen in either soft or skeletal tissues of pups at term from treated dams did not differ significantly from those seen from sham-treated dams.

"However, as has been reported previously in connection with similar materials administered to this species, a dose-related maternal toxicity was evident (cf Table 1). The observed mortality approached 50 per cent (at 700 mg/kg) with the majority of deaths occurring late in the dosing period or after dosing had been completed. Anorexia was a marked sign during a period of from 48 to 72 hours prior to death. Most of the animals found dead were not pregnant. Those which did survive appeared normal throughout the observation period and bore normal young.

It is concluded that the test material is not a teratogen for the rabbit.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 81 through 86

Material : FDA 71-16

Date: May 31, 1973

Laboratory No. : 0896 f

Table 1

Fate Summary
(Rabbits)

Group	Material	Dose mg/kg	Total			Surviving at Term	
			Mated	Died[1]	Pregnant	Total	Pregnant[2]
81	Sham	0.0	14	0	10	14	10
82	6-AN*	2.5	12	0	11	12	11
83	FDA 71-16	7.0	14	1	10	13	10
84	FDA 71-16	33.0	14	2	12	12	10
85	FDA 71-16	150.0	14	2	10	12	10
86	FDA 71-16	700.0	21	9	14	12	9

* Positive Control : 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

** Administered as a corn oil solution (See Appendix I)

1 After Day 6 and before term

2 Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 81 through 86
Material: FDA 71-16

Table 2
Reproduction Data
(Rabbits)

Date: May 31, 1973
Laboratory No.: 0896 f

Group:	81	82	83	84	85	86
Dose (mg/kg):	Sham	6-AN**	7.0	33.0	150.0	700.0
Pregnancies						
Total No.	10	11	10	12	10	14
Died or Aborted (before Day 29)	0	0	0	2	0	5
To term (on Day 29)	10	11	10	10	10	9
Corpora Lutea						
Total No.	189	151	154	207	170	247
Average/dam mated	14.5	12.6	11.9	14.8	13.1	11.8
Live Litters						
Total No.*	10	8	10	8	9	9
Implant Sites						
Total No.	71	54	60	70	78	47
Average/dam*	7.10	4.91	6.00	7.00	7.80	5.22
Resorptions						
Total No.*	11	16	9	13	13	4
Dams with 1 or more sites resorbed	3	7	4	6	5	3
Dams with all sites resorbed	--	2	--	2	1	--
Per cent partial resorptions	30.0	63.6	40.0	60.0	50.0	33.3
Per cent complete resorptions	--	18.2	--	20.0	10.0	--
Live Fetuses						
Total No.	59	37	51	55	65	43
Average/dam*	5.90	3.36	5.10	5.55	6.50	4.78
Sex ratio (M/F)	0.72	0.36	0.72	0.88	0.61	1.26
Dead Fetuses						
Total No.*	1	1	--	2	--	--
Dams with 1 or more dead	1	1	--	1	--	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	10.0	9.09	--	10.0	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	37.1	34.4	37.8	33.6	37.0	38.7

* Includes only those dams examined at term.
** Positive Control: 6-aminonicotinamide dosed on Day 9 (2.5 mg/kg)

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 81 through 86 — Laboratory No. 0896 f

Table 3

Material FDA 71-16 — Date May 31, 1973

Summary of Skeletal Findings* (Rabbits)

Findings / Group No.	81	82	83	84	85	86
Dose (mg/kg):	Sham	6-AN**	7.0	33.0	150.0	700.0
Live Fetuses Examined (at term)	51/10	36/7[a]	51/10	50/8	67/9	44/9
Sternebrae						
Incomplete oss.			1/1	2/2	3/1	1/1
Scrambled						
Bipartite						
Fused	2/2	5/4	1/1	2/2	2/2	1/1
Extra	1/1		2/2	3/2	3/2	1/1
Missing						
Other						
Ribs						
Incomplete oss.						
Fused/split		11/5				
Wavy						
Less than 12						
More than 13						
Other						
Vertebrae						
Incomplete oss.						
Scrambled		7/4				
Fused						
Extra ctrs. oss.						
Scoliosis		9/3				
Tail defects		35/7				
Other						
Skull						
Incomplete closure						
Missing						
Craniostosis		1/1				
Other						
Extremities						
Incomplete oss.						
Missing						
Extra						
Miscellaneous						

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.

** Positive control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9.

[a] One litter lost in processing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 81 through 86 Date May 31, 1973

Material FDA 71-16 Laboratory No. 0896 f

Table 3-a
Summary of Soft Tissue Abnormalities
(Rabbits)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
82	6-AN*	2.5	Z 6121	1	Anopia
			Z 6122	4	Anopia; short tail
			Z 6123	4	Anopia
			Z 6125	7	Anopia; medial rotation hind limbs; short tail
			Z 6127	8	Anopia
			Z 6128	1	Club foot
				1	Cleft palate

* Positive Control: 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 81 through 86

Species Rabbits

Table 4

Average Body Weights*

Date May 31, 1973

Laboratory No. 0896 f

Group	Material	Dose Level	Day 0	6	12	18	29**
		mg/kg	kg				
81	Sham	0.0	2.41	2.51	2.55	2.60	2.67 (10)
82	6-AN***	2.5	2.28	2.33	2.34 (11)	----[a]	2.45 (10)[b]
83	FDA 71-16	7.0	2.34	2.43	2.47	2.41 (10)	2.46 (9)[c]
84	FDA 71-16	33.0	2.42	2.46	2.38	2.46	2.51 (10)
85	FDA 71-16	150.0	2.16	2.26	2.28	2.35 (10)	2.45 (9)[c]
86	FDA 71-16	700.0	2.54	2.48	2.61	2.60	2.81 (9)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 6-aminonicotinamide dosed on day 9
a Weights not recorded for Day 18
b Average weights of 10 dams on Day 29 (Final weight of one dam not recorded)
c Average weight of 9 dams on Day 29 (Final weight of one dam not recorded)

Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20 x 10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

Dosage (mg/kg)	Dose (ml/kg)	Concentration (mg/ml)
≦ 250	1	≦ 250
251 - 500	2	125 - 250
501 - 750	3	133 - 250
751 - 1000	4	187 - 250
1001 - 1250	5	200 - 250
1251 - 1500	6	208 - 250
1501 - 1600	6.4	235 - 250

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 81

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0896

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 6121	P	14	7	7		3	4		36.8	
S 6122	P	14	8	8		4	4		36.0	
S 6123	P	--**	7	7		3	4		40.6	
S 6124	NP	9	0						----	
S 6125	P	22	9	9		4	5		38.3	
S 6126	NP	14	0						----	
S 6127	P	11	7	2	1	0	2	4	36.3	
S 6128	P	34	9	9		--**	--**		40.4	
S 6129	P	20	9	3		1	2	6	37.8	
S 6130	NP	13	0						----	
S 6131	NP	8	0						----	
S 6132	P	11	4	4		2	2		43.2	
S 6133	P	9	7	6		2	4	1	19.8	One neonatal death
S 6134	P	10	4	4		2	2		42.2	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 82

Material 6-AN

Dose 2.5 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0896

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Z 6121	P	11	1	1		0	1		42.0	
Z 6122	P	13	7	4		1	3	3	34.4	Four neonatal deaths
Z 6123	P	10	6	4		2	2	2	39.1	Four neonatal deaths
Z 6124	P	9	3					3	----	
Z 6125	P	16	7	7		--**	--**		34.0	Three neonatal deaths
Z 6126	P	19	5	5		1	4		31.8	Two neonatal deaths
Z 6127	P	19	11	8		2	6	3	31.5	Five neonatal deaths
Z 6128	P	10	6	4		1	3	2	29.3	Three neonatal deaths
Z 6129	P	16	4	4		1	3		33.1	Three neonatal deaths
Z 6130	P	16	2					2	----	
Z 6131	NP	5	0						----	
Z 6132	P	7	2		1			1	----	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 83

Material FDA 71-16

Dose 7.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0896 f

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
F 6001	NP	--**	0						----	
F 6002	P	11	6	6		3	3		37.1	
F 6003	P	12	6	6		2	4		37.5	
F 6004	NP	6	0						----	
F 6005	P	11	6	6		2	4		37.3	
F 6006	P	21	8	8		2	6		33.8	One neonatal death
F 6007	P	11	4	1		--**	--**	3	38.1	
F 6008	P	13	5	4		1	3	1	36.2	
F 6009	P	13	5	5		3	2		32.0	
F 6010	P	13	4	4		2	2		44.0	
F 6011	NP	5	0						----	
F 6012	NP	11	0						----	Died Day 14
F 6013										Not Assigned
F 6014	P	12	6	5		3	2	1	38.2	
F 6015	P	15	10	6		3	3	4	43.5	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 84

Material FDA 71-16

Dose 33.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0896 f

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
F 6016	P	8	4	4		2	2		40.4	
F 6017	P	15	8	--		--	--		----	Died Day 18
F 6018	P	10	5	1		1	0	4	33.1	
F 6019	P	7	4					4	----	
F 6020	P	17	9	9		--**	--**		33.9	
F 6021	NP	5	0						----	
F 6022	P	20	9	8		--**	--**	1	34.4	
F 6023	P	5	5	--		--	--		----	Died Day 25
F 6024	NP	5	0						----	
F 6025	P	20	9	9		4	5		27.5	One neonatal death
F 6026	P	16	9	8		4	4	1	34.1	
F 6027	P	24	7	6		--**	--**	1	----**	
F 6028	P	36	4		2			2	----	One neonatal death
F 6029										Not Assigned
F 6030	P	19	10	10		4	6		31.7	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 85

Material FDA 71-16

Dose 150.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0896 f

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
F 6031	P	15	11	11		5	6		38.7	
F 6032	P	14	7	7		3	4		45.8	
F 6033	P	12	6	4		2	2	2	36.2	
F 6034	P	13	7					7	----	
F 6035	NP	13	0						----	Died Day 24
F 6036	P	13	6	6		2	4		38.7	
F 6037	P	23	8	6		2	4	2	38.1	
F 6038	NP	7	0						----	
F 6039	P	13	7	7		--**	--**		33.2	Two neonatal deaths
G 6040	NP	5	0						----	
F 6041	NP	--**	0						----	Died Day 26
F 6043	P	16	9	9		3	6		40.8	
F 6046	P	13	8	7		3	4	1	25.6	
F 6047	P	13	9	8		2	6	1	35.5	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 86

Material FDA 71-16

Dose 700.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0896 f

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
F 6046	P	4	3	3		2	1		34.7	
F 6047	P	8	4	4		2	2		36.2	
F 6048	P	11	6	--		--	--		----	Died Day 26
F 6049	P	10	4	4		2	2		36.4	
F 6050	NP	4	0						----	Died Day 28
F 6051	NP	15	0						----	Died Day 17
F 6052	NP	4	0						----	Died Day 18
F 6053	P	15	7	--		--	--		----	Died Day 18
F 6054	NP	6	0						----	
F 6055	NP	7	0						----	
F 6056	NP	21	0						----	Died Day 18
F 6057	P	11	8	7		4	3	1	39.9	
F 6058	P	8	6	--		--	--		----	Died Day 11
F 6059	P	19	6	6		4	2		45.3	
F 6060	NP	11	0						----	
F 6061	P	25	10	--		--	--		----	Died Day 17
F 6062	P	14	5	4		3	1	1	43.9	
F 6063	P	9	7	--		--	--		----	Died Day 28
F 6064	P	15	5	5		3	2		34.5	
F 6065	P	21	11	9		3	6	2	34.3	
F 6072	P	9	1	1		1	0		43.4	

* P = Pregnant; NP = Not Pregnant